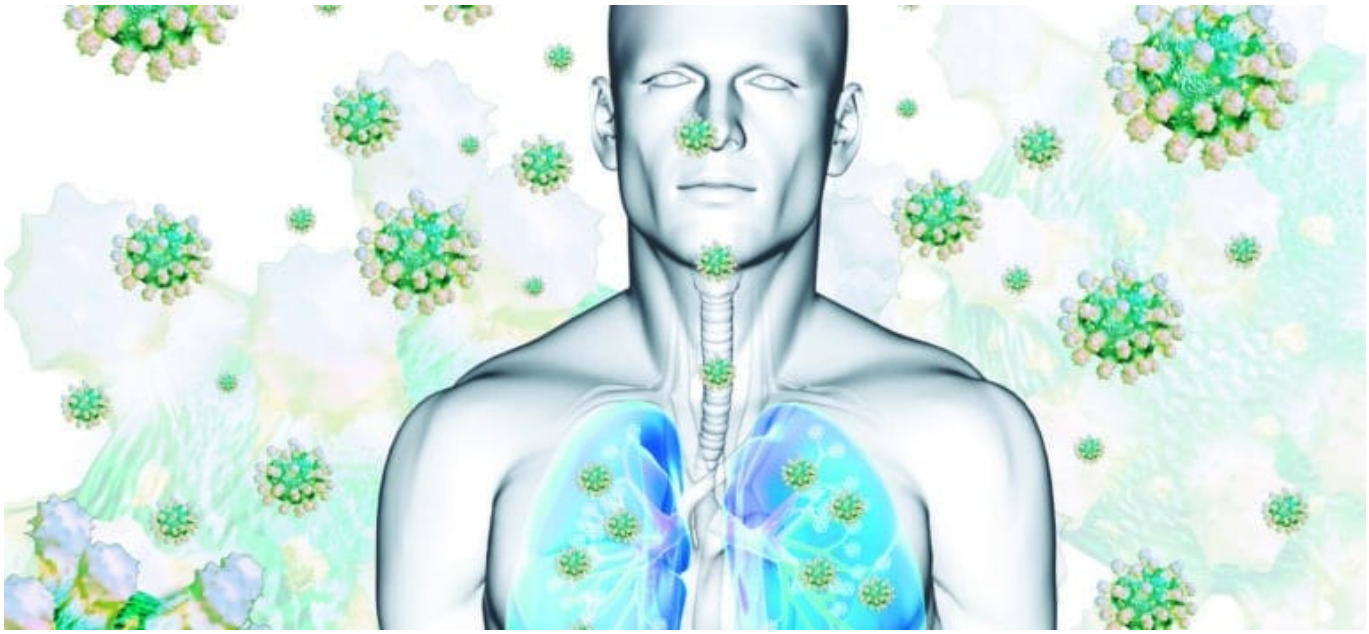
Exploring MS origins



2023 Dystel Prize winner focuses on how the immune system could fight off the disease

by Vicky Uhland

When he was a secondary school student near Würzburg, Germany, in the 1970s, Roland Martin, MD, never envisioned that his future would include becoming one of the world's leading researchers on multiple sclerosis. In fact, he wasn't sure he wanted a career in medicine at all.

Roland Martin, MD

"The options I was interested in were being a doctor or an architect. But then I discovered I

couldn’t draw very well,” he says with a smile.

Martin put his drafting table aside and enrolled in the University of Würzburg Medical School. After earning his medical degree in 1983, he did postdoctoral research with one of his professors, a pediatrician, virologist and immunologist.

Heavily influenced by this work, Martin planned to become a pediatrician. But once again, circumstances intervened. There were no pediatric medical residencies available at that time, so he opted for his second choice: neurology.

It turned out to be an auspicious decision, launching a career as an MS physician-scientist that has been so influential that Martin has been named the 2023 recipient of the prestigious John Dystel Prize for Multiple Sclerosis Research.

The Dystel Prize has been awarded annually by the National Multiple Sclerosis Society and the American Academy of Neurology since 1995. This $40,000 prize recognizes significant and exciting contributions to MS research that have changed the way we think about multiple sclerosis treatment and prevention.

“Roland Martin is a remarkably creative physician-scientist and neurologist whose brilliant investigations have profoundly advanced knowledge of the fundamental biology of MS,” says Stephen Hauser, MD, who won the Dystel Prize in 2008.

“[Martin’s] discoveries — bridging genetics, epidemiology and immunology — revealed how inheritance, coupled with critical environmental exposures, can lead to a misdirected immune attack against the nervous system. He has given us a new understanding of how MS might begin.”

Combining the bench and the bedside

Martin has investigated MS origins, treatments and potential cures as a clinician and researcher, which he believes has improved his work in both areas.

As a clinician, he’s worked with people with MS in Germany, the United States, Spain and Switzerland. He helped build MS centers for patient care at the University of Hamburg and University Hospital Zurich. Martin also served as the head of the Zurich MS center, supervising a large group of caregivers and spending about 50–60% of his day with people with MS.

“It’s highly motivating to interact with patients and learn firsthand what their needs and thoughts are,” he says, noting that while he’s not as well-trained in scientific methods as PhDs are, his work with patients helps him formulate key questions to answer in his research.

In fact, much of his research is geared toward answering a question people with MS have been asking for decades: What triggers the immune attacks on the brain and spinal cord in MS?

“The two main research lines I’ve always been interested in are mechanisms of the disease and trying to develop treatments,” Martin says. “If you influence the immune system, you learn about the mechanisms of the disease, and that leads to developing treatments.”

Restoring balance

In the 1960s and ’70s, Martin said researchers noted that more MS relapses tended to occur when a person had a viral infection like a cold, leading scientists and clinicians to focus on viruses and MS. But when Martin began his research into MS in the late 1980s, that thinking had shifted. MS was regarded more as an autoimmune disease than due to viral infection.

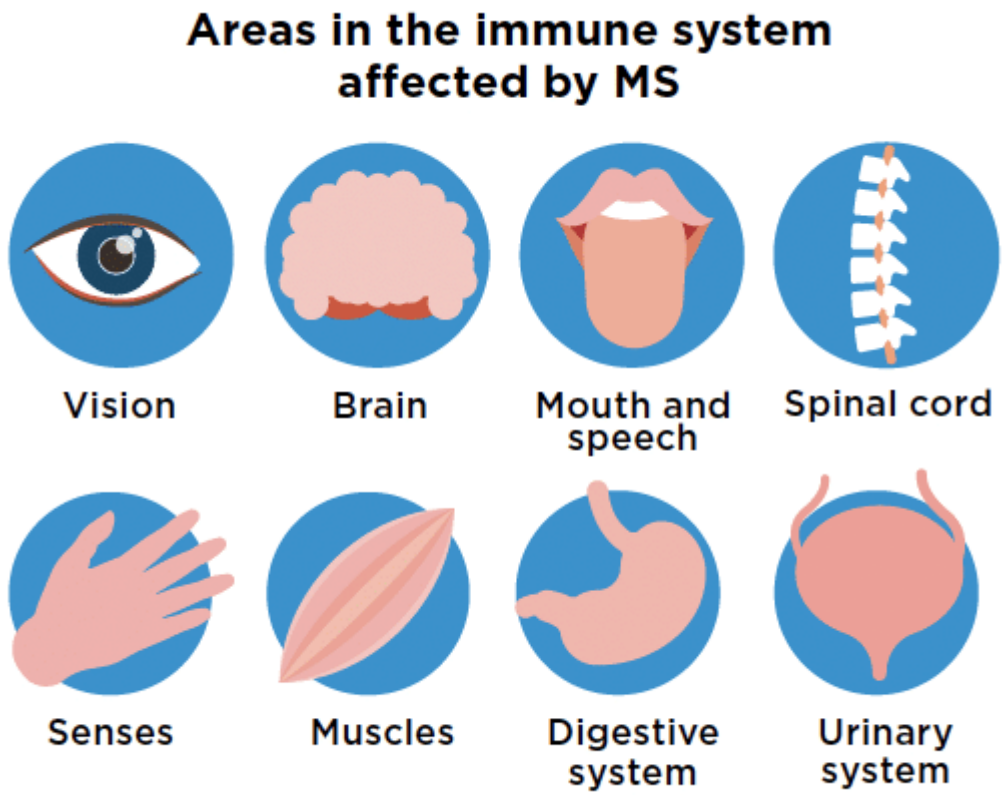
It’s now widely accepted that a misguided immune response can turn against the nervous system in people with MS and exacerbate the disease. But when Martin was a young researcher, no one really understood why or how this happens.

“You need to know what the target is, what the immune system needs to fight,” he says.

Martin’s early research at institutions in Germany and at the National Institutes of Health in the U.S. focused on what’s essentially a knife’s edge between tolerance and attacks on the body’s own tissues. Normally, the immune system produces white blood cells that fight viruses and other infectious diseases. When the immune system is out of balance, it can lead to immune-mediated diseases like MS. Martin’s long-term goal has been to figure out ways to restore that balance and turn off specific immune cells that cause MS — a concept called immune tolerance.

Learning about immune tolerance

Martin’s research on target antigens in MS pursued two goals: 1) to understand which parts of the central nervous system are attacked by autoreactive T cells, and 2) how this knowledge could be used to silence the misdirected immune response and restore tolerance.



One of those studies focused on a specific protein found in myelin in people and animals. The study — led by Lawrence Steinman at Stanford, a former Dystel prize winner — had shown that a modified version of a myelin protein turned off the autoimmune reaction in an animal model of MS. But in a human trial, Martin and his team discovered that the treatment actually made MS worse in three out of the eight people studied, which led to an immediate halt of the trial.

“We were very disappointed, frustrated and upset that we had caused harm to patients,” he says. “It was a very important lesson.”

But the study wasn’t entirely a failure. It taught researchers that this specific myelin protein (called an antigen) was key to the immune reaction in at least some people with MS. Martin and others are now using that knowledge to develop more targeted, safer approaches to turning off the immune system in people with MS.

That includes groundbreaking research Martin’s currently working on that may lead to the ability to stop MS in its early stages — without the side effects of medications.

Preventing MS with an injection?

This research, known as immune tolerance induction, involves extracting red blood cells from an individual with MS, mixing them with myelin antigens and other autoimmune antigens, and then injecting them back into the individual.

Old red blood cells routinely die in the body and are replaced with new cells. The same happens with Martin’s doctored red blood cells. The research is designed to see if the human immune system views these antigen-coupled, dying cells in the same way it views regular

red blood cells, and consequently doesn't mount an immune response. In essence, the immune system would be trained to ignore the MS target antigen that had been glued onto red blood cells in people with MS, and not trigger the disease.

A more drastic way of restoring immune tolerance is autologous haemopoietic stem cell transplant (aHSCT) therapy — indeed, Martin's research was instrumental in Switzerland's recent approval of aHSCT for people with aggressive MS.

Like aHSCT, the tolerance-inducing therapy — which has been named RED4MS — will re-establish a tolerant immune system in people with MS. But RED4MS is not as invasive as aHSCT, which employs cytotoxic drugs to eliminate the entire immune system first and then re-establishes a new one from hematopoietic stem cells. Instead, RED4MS involves extracting red blood cells from a person via a simple blood draw. RED4MS is also more specific than aHSCT, which resets the entire immune system.

Martin said, in studies so far, RED4MS does not seem to have the side effects of aHSCT, including loss of fertility in up to 30% of patients. aHSCT is also not a good option for people with mild disease, whereas RED4MS could potentially be used in a variety of individuals with MS, even in its earliest stages.

Martin says the first trials with RED4MS have shown evidence of safety and tolerability in MS patients. Furthermore, studies in the laboratory indicate that it eliminates the autoimmune T cells. In lab animals, a single tolerization treatment like RED4MS completely eradicates the MS-like disease, but whether the same will also be found in humans will require further research.

In 2023, the biotech startup that Martin, Andreas Lutterotti and team launched began a 1.5-year trial of RED4MS in more than 20 MS centers in four European countries. If the trial is successful, it could usher in an exciting new way to treat or even prevent MS.

"It's something immunologists have dreamed about for more than five decades, but most attempts have failed," Martin says.

Looking to the future

When Martin began his neurology residency in 1985, there wasn't a single treatment for MS.

No MS treatment is perfect. They all have side effects, including the potential to compromise the immune system and make people vulnerable to infections. Martin says one of the issues is that current MS treatments focus on the inflammatory aspects of the disease and inhibit the immune system, but there's nothing that actually protects cells or prevents someone from getting the disease in the first place.

"In MS, all treatments consist of single drugs that target one aspect of the disease," he says. "The most obvious combination for future therapies would be something that blocks the immune system and another drug that protects nerve cells and cells in the brain from

damage.”

For 15 years, Martin has been looking at an approach that could potentially achieve this. He’s been researching hydroxytyrosol, an amino acid derivative and strong natural antioxidant found in olives, but also produced in our brains in small quantities. Hydroxytyrosol is well tolerated and has shown positive effects in animal models and cell culture, but financing is needed to conduct human trials. It could be one approach to protect cells of the brain.

In the meantime, Martin and his team will continue the development of RED4MS through a company he, Lutterotti and colleagues — including his wife, immunologist Mireia Sospedra, PhD — operate in Switzerland.

He has also cofounded a company in Boston to pursue research on using beneficial T cells to treat the disease.

“Rather than eliminating the bad T cells, we enhance the good ones,” Martin says. He anticipates human clinical trials will begin in 2024.

Vicky Uhland is a writer and editor in Lafayette, Colorado.